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ARE MALIGNANT GROWTHS ARISING FROM PIGMENTED MOLES OF A CARCINOMATOUS OR OF A SARCOMATOUS NATURE?—REPORT OF TWO CASES (ONE IN A NEGRO) WITH A STUDY OF THE HISTOGENESIS OF PIGMENTED MOLES.

BY

T. CASPAR GILCHRIST, M.R.C.S.,

Clinical Professor of Dermatology, Johns Hopkins University and Hospital; and Clinical Professor of Dermatology, University of Maryland.

REPRINTED FROM THE JOURNAL OF  
CUTANEOUS AND GENITO-URINARY DISEASES,  
FOR MARCH, 1899.



ARE MALIGNANT GROWTHS ARISING FROM PIGMENTED MOLES OF A CARCINOMATOUS OR OF A SARCOMATOUS NATURE?—REPORT OF TWO CASES (ONE IN A NEGRO) WITH A STUDY OF THE HISTOGENESIS OF PIGMENTED MOLES.<sup>1</sup>

BY T. CASPAR GILCHRIST, M.R.C.S.,

Clinical Professor of Dermatology, Johns Hopkins University and Hospital; and  
Clinical Professor of Dermatology, University of Maryland.

(From the Pathological Laboratory of the Johns Hopkins University and Hospital.)

MALIGNANT melanotic growths arising from pigmented moles have generally been considered to be of a sarcomatous nature. This opinion is based partly upon the histological structure of the growths partly upon their apparent identity with the undoubtedly sarcomatous tumors springing from the choroid coat of the eye and partly upon the belief that the moles themselves are essentially of connective-tissue origin, and that, therefore, cellular tumors developing from them are to be regarded as sarcomatous.

Opposition to these previously accepted views was raised by Unna in 1892, who, in his investigations of the histogenesis of pigmented moles, came to the conclusion that the cells in the corium which make the most characteristic constituents of the moles are derived from the rete layer of the epidermis and not from endothelial or connective-tissue cells. Unna reached this result mainly by the study of moles in early stages of their development in infants, whereas previous observations had related mostly to quiescent, fully developed moles in which, according to Unna, it is usually difficult or impossible to determine the exact source of the large epithelioid cells composing them.

In accordance with the present histogenetic classification of tumors it is evident that if the cells in pigmented moles which give rise to the so-called melanotic sarcomata are in reality of epithelial origin, then these tumors are to be transferred from the group of sarcomata to that of epitheliomata or carcinomata, and this is the position taken by Unna.

Since the publication of Unna's researches upon this subject, divergent opinions have been expressed as to the accuracy of his conclusions. Green and Bauer were unable to confirm Unna's observations

<sup>1</sup> Read before the Twenty-second Annual Meeting of the American Dermatological Association, June, 1898.

whereas Scheuber's results are in harmony with those of Unna. The subject is evidently one needing further investigation.

The study of the two present cases, together with the histological examination of numerous moles, would seem to justify an expression of opinion of this subject.

So far as the records in the literature go but very few cases of this kind have been reported in this country and among them I have been able to find only two instances in negroes, in neither of which was there any microscopical examination.

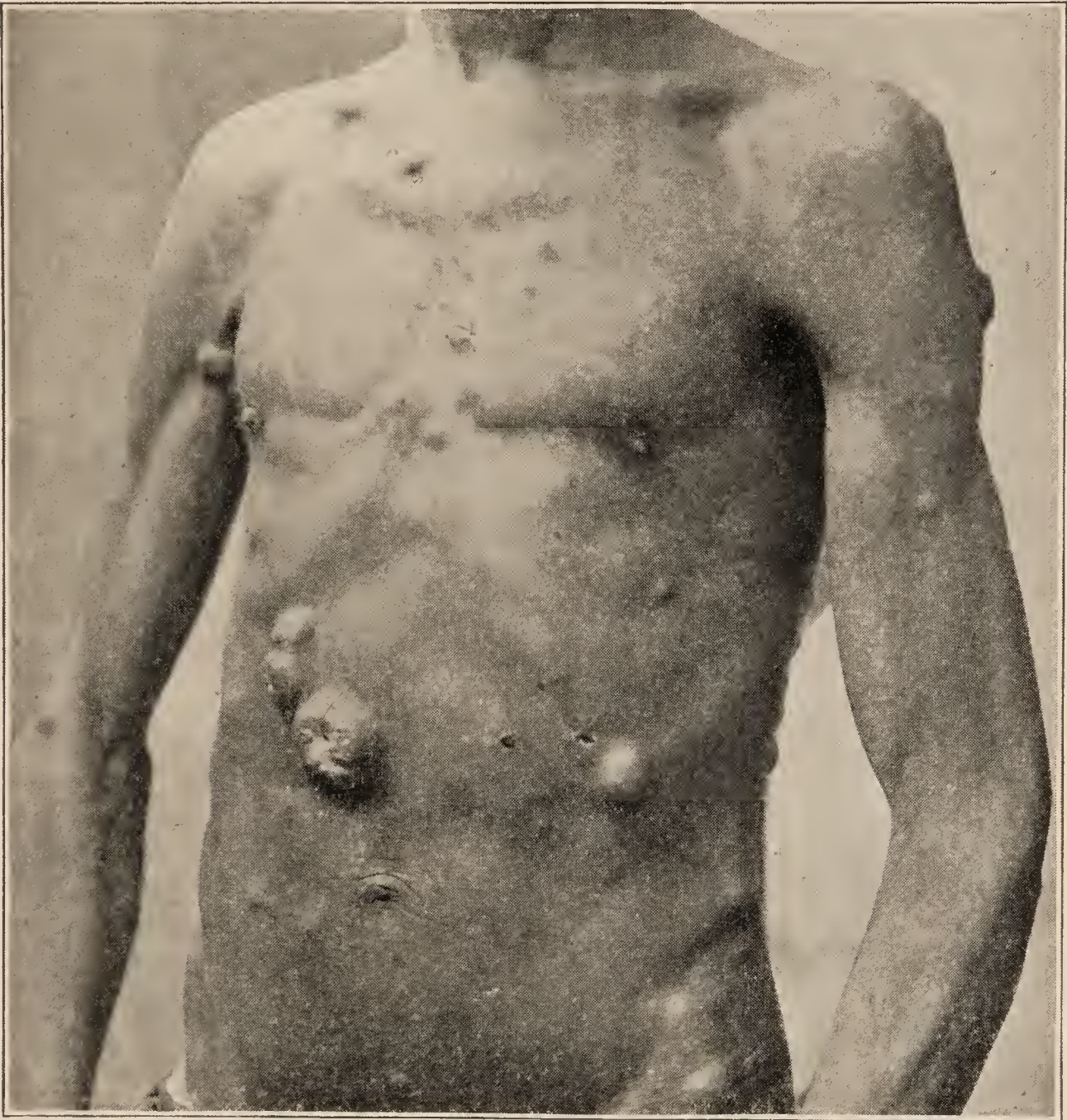
CASE I.—The patient was a full-blooded negro, fifty-eight years old, about 5 feet 9 inches in height and married. Family history negative. With the exception of the ordinary diseases of childhood the patient had always enjoyed exceptionally good health previous to the present disease.

About four years ago, while washing, he noticed a small, very black spot on the sole of the right foot, situated about 2 cm. behind the root of the second toe. But little attention was paid to this spot, as it was unaccompanied by any pain, stiffness or difficulty in using the foot. The patient gave a history of accident to the foot three years previous to the appearance of the lesion but there does not appear to have been any connection between the two, as the injury at that time had been to the dorsum of the foot. The pigmented patch grew very slowly in size; it also began to get harder and to be slightly raised. The patient took it for an ordinary corn and as it began to annoy him on account of its position, he cut it with a razor, with the result that a watery fluid oozed out. The lesion now began to grow much more rapidly and three years ago he consulted Dr. M. D. Brown of this city, who described it (to the writer) as a deeply pigmented patch about the size of a "nickel" (a little less than 2 cm. in diameter), only slightly raised and presenting an appearance of ulceration in the center. After this the growth kept on increasing, but not very rapidly, so that, according to the patient's account, after two years it had reached the size of one of the secondary growths which was found on the abdomen when he came to us and which measured 4 x 4 cm. All this time he had continued at his work as a laborer. The first metastasis was noticed two years after the "corn" first appeared; it was situated on the same leg a little below the knee. Just before the secondary nodule appeared the patient had been operated upon by a local physician, who removed the primary growth, which, however, soon recurred. After the secondary growth (eighteen months ago) appeared the patient was again operated upon by Dr. Cole of this city, who removed both the primary and secondary growths, since which time there has been no recurrence

of these two lesions. Up to this time the patient's general health had been excellent. He first came under notice at the University of Maryland in December, 1897, and his condition was then as follows:

On the *sole of the right foot* there was a linear scar which was situated just posterior to the big toe. The metastases were distributed

FIG. 1.



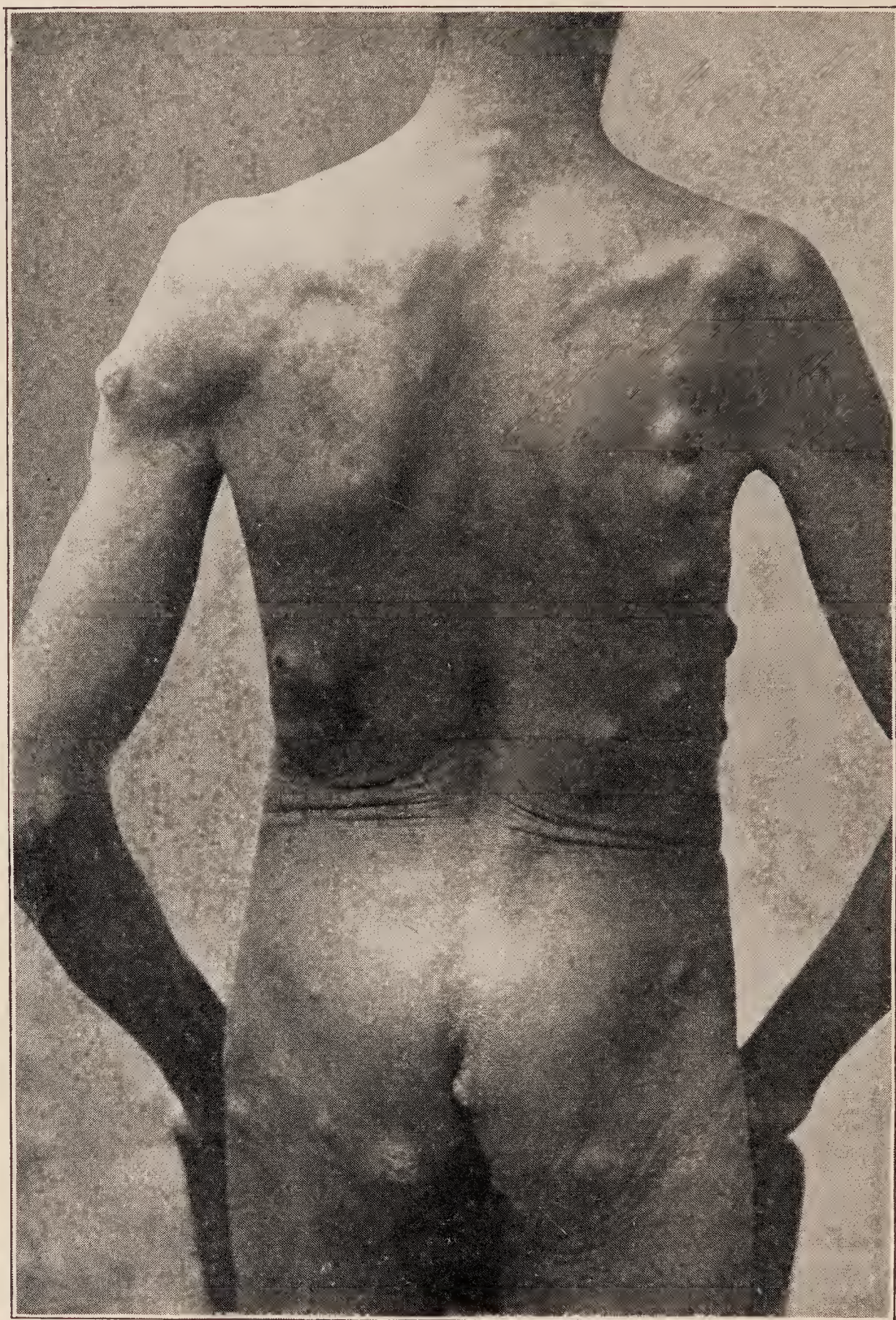
Melanocarcinoma in skin of negro.

on the trunk and extremities, but the head, neck, and mucous membranes of the mouth, nose, and eyes were all normal.

On the *left upper extremity* nodules were present only on the upper arm. One nodule, 3 x 3 cm., was attached to the skin overlying it; the latter presented a purplish-black, irregular, shiny surface with three small scales. There were two smaller tumors 5 x 5 mm., both attached to the skin, one above and one below the insertion of the deltoid; a third

of similar size, which was just commencing to involve the skin, was found just above the border of the axilla. The presence of the smallest

FIG. 2.



Melanocarcinoma in skin of negro.

growth was only recognized after feeling the skin carefully; it was about the size of a mustard-seed; it was quite firm, deeply situated, and perfectly movable beneath the skin.

The *right upper extremity* also presented lesions only above the elbow. One nodule, near the external condyle, measured about 1.5 x 1.5 cm.; it was lobulated and was just commencing to be attached to the skin, which was tense and more deeply colored than normal. There were three other growths, varying from a mustard-seed to a pea in size in this region; they presented features similar to those described in speaking of the nodules on the left arm.

On the *chest* was a nodule the size of a mustard-seed, situated just above the left clavicle; the growth was firm, deeply situated, and very movable beneath the skin. A similar nodule was found over the right clavicle, and just below the clavicle another could be felt which was so movable that it could be pushed over the bone. On the anterior surface were scattered fourteen nodules varying in size from that of a mustard-seed to that of a pea. Those of the smallest diameter could not be detected by the eye, but could only be felt. Wherever a growth was slightly larger, a small, apparently papular, elevation of the skin could be noticed.

On the *abdomen*, between the umbilicus and ribs, a little to the right, were two large masses. The lower one measured 4 x 4 cm.; it rose abruptly 1 cm. in height above the normal skin and the center showed an irregular, excavated, rather dry ulcer. The growth was very firm, deeply pigmented, and could be lifted up from the underlying structures. No pus could be squeezed from the ulcer. The upper tumor, which was made up of two nodules which had fused together, measured 4 x 2 cm. It presented an elevation of 1 cm. and its upper portion was broken down whereas the lower had only implicated the skin but was deeply pigmented. Scattered over the abdomen were eight other nodules varying in size from 1 to 2 cm. in diameter and of a character similar to those already described. Photograph, Fig. I., shows most of the nodules scattered over the anterior surface of the trunk and arms.

On the back, as shown in photograph, Fig. II., were scattered twenty-nine nodules of various sizes and in different stages of growth; they were all of a firm consistence. On the right side were six running almost in a vertical line directly downward from the shoulder. There was also a group of five situated toward the left side between the eighth and tenth ribs.

The buttocks showed ten tumors of various sizes; only two of them were beginning to implicate the skin and were deeply pigmented. On each thigh were four nodules of medium and small size. Four were scattered over the surface of the right leg. One small growth was situated over the tarso-metatarsal joint of the big toe on the dorsal surface.

Generally speaking, on palpating the smallest nodules, which could only be found after careful searching, these were always found to be in the deepest portion of the skin; they were freely movable beneath the skin and over the underlying structure. They were very firm and were suggestive of a mustard-seed embedded in the subcutaneous tissue. It was only when the nodules reached a size of about 3 mm. in diameter that there was slight indication to the eye of its presence in the deeper structures, evidenced on the surface by what appeared to be a papule. Before the skin became involved the nodule had grown to quite a large size, from 1.5 to 2 cm. in diameter. The skin overlying the growth did not become pigmented until the latter became attached to it. When ulceration occurred it was a dry ulceration and no pus appeared to be present. No enlarged lymphatic glands were observed in any portion of the body. The patient did not complain of any pain, even when the nodules were handled. He complained of some bladder disorder and had entered the hospital more for this trouble than on account of the secondary nodules. His general condition was poor and he was emaciated. Both eyes were perfectly normal. One of the nodules was cut into for macroscopic examination and the center was found to be deeply pigmented. A diagnosis of melanotic sarcoma was made.

A number of the smaller nodules were afterward excised for histological examination. The patient was put on hypodermic injections of Fowler's solution, commencing with 1 minim a day, the dose being increased each day. He left the hospital of his own accord after three-weeks' treatment. No improvement had taken place. The urine contained melanogen.

The patient was seen at his home occasionally during the eight months previous to his death and during that time hundreds of metastases appeared over the various regions of his body, but what was rather remarkable, no involvement of the lymphatic glands occurred.

One month before death a medium-sized nodule was partly removed after burning the surface and the excised portion was placed in a sterile Petri dish. The tissues were teased thoroughly in sterile bouillon, which was poured into the Petri dish, and the mixture was inserted through a pipette into the external jugular vein of a dog. The animal seemed to thrive and become very vigorous; after two months it was killed. Nothing abnormal could be discovered either in the lungs or neighboring glands, or locally.

From the history of this case there does not appear to be any doubt that this pigmented malignant growth had its origin in the skin of the sole of the right foot, and that it probably resulted from some previous pigmented mole, although the patient says he had never noticed any

present. The physician who first saw the patient was convinced that it was a purely cutaneous lesion, deeply pigmented and slightly ulcerated. It may safely be concluded, therefore, that the lesion began in an area of the skin, which in the negro is less pigmented than the rest of the surface of the body, namely, the sole of the foot. The metastases began to make their appearance only after the growth had been cut by the patient.

Although no portion of the primary growth could be obtained for microscopical examination, a number of the metastatic growths in various stages of development were excised. The smallest nodule, which was just perceptible to the touch and which felt like a small mustard-seed embedded in the subcutaneous structure, was excised and the sections showed the following changes. Fig. 3 represents one of the sections. The epidermis (*E*) and the whole of the corium (*C*) were practically normal. The most striking change was the presence of a metastatic nodule (*M*) 1 mm. in diameter in the lower portion of the subcutaneous tissue (*T*). Besides this nodule and some pathological changes along its upper and lateral margins the subcutaneous area, as well as the whole of the corium and epidermis in the section, showed practically nothing abnormal except an enlargement of the veins (*V*). The metastatic nodule is oval in shape and sharply defined. Along the lower margin there is a tendency to the formation of fibrous tissue but along the upper margin and especially where it is in contact with the fat-cells (*A*) there are large numbers of round mononuclear cells, many of which are plasma-cells. The nodule is made up almost entirely of epithelioid cells; the majority are mononuclear, although quite a number are multinucleated. The cells vary very much in size and shape according to the pressure exerted upon them. The large multinucleated cells are situated nearer the center of the nodule. The nuclei also vary very much in size and shape, some being very large; a number of nuclear figures can be observed. Many nuclei present vacuoles of various sizes; others present large numbers of deeply staining, variously sized granules. Toward the center of the growth as well at the periphery are many young epithelioid cells. Between the epithelioid cells throughout the whole of the metastatic growth are scattered comparatively few lymphoid cells. Where the tumor encroaches on the fat-cells single epithelioid cells were found advancing between the fat-cells and accompanied by numerous lymphoid cells as well as some plasma cells. Fine connective tissue and connective-tissue cells run between groups of the epithelioid cells. The fat-cells which have been replaced by the growth disappear. In one section at the margin could be seen one large multinucleated epithelioid

cell which had advanced among the fat-cells; this epithelioid cell was thickly surrounded by lymphoid cells and a few polynuclear leucocytes. Pigment masses, pigment cells, and pigment granules are already present in the metastasis, chiefly in the lower and central portion of the nodules. At this stage the pigment is not present in large amount. No blood-vessels are to be seen within the nodules.

Another metastatic growth excised was a little larger than the previous one, measuring a little over 2 mm. in diameter. The section showed that the increase in size had taken place chiefly in an upward and lateral direction. The amount of pigment was increased and the collection of lymphoid cells at the upper and lateral margin was denser. The next two metastases which were removed measured respectively 3 and 4 mm. in their longest diameter. The pigment masses in the form of cells have now begun to assume large proportions and appeared to enter the nodule from below. The nodule was still increasing in size along the upper and lateral margin almost exclusively, *i.e.*, in the direction of least resistance. The collection of lymphoid cells, seen at the junction of the fat lobule in the smaller metastases, was not nearly so noticeable in these sections.

The larger nodules did not present anything strikingly different from those already described. The increase in size had always been rapid in the upward direction until the skin was reached. The growth had become more and more pigmented as it increased in size and when the nodule reached the epidermis, very pronounced masses of pigment cells, many of which had an epithelioid character, were situated between the nodule and the epidermis.

The character of the epithelioid cells, of the nuclei, and the arrangement of the cells (alveolar) is practically the same up to the time the nodule reaches its largest size. The adjoining tissues are disturbed only mechanically and even when the nodule begins to implicate the epidermis there are practically no collections of lymph or plasma cells such are seen in the commencing nodules. There are also but few lymphoid cells scattered throughout the nodule itself, except in the center, where collections of them are found. Many forms of degenerating cells are seen.

The epidermis gives way as the metastatic growth goes on increasing in size, so that finally a dry ulcer is formed.

CASE II.—I am particularly indebted to Dr. Young of the Johns Hopkins Hospital for the privilege of recording this case. It was of special interest because the lesion was excised in an early stage of its growth and because it afforded the best opportunity for demonstrating

that this malignant overgrowth originating from a pigmented mole was a melanotic carcinoma, and not a sarcoma.

The patient, a physician, gave the following history: About seven years ago there gradually appeared on the left cheek, just below the eye and near the nose, a pigmented mole which was very small at first; it increased very slowly in size for five years, at which time it had attained



Section of the earliest perceptible cutaneous metastasis in Case I. of melanocarcinoma. *M*, nodule situated in the subcutaneous tissue, *T*; *A*, the collection of lymphoid and plasma-cells aggregated at the periphery of the nodule; *E*, the epidermis; *C*, the corium, and *T*, the subcutaneous tissue; *H*, a hair-follicle; *V*, the blood-vessels; *S*, the sweat-glands; *A*, an artery; *F*, the fat lobules; *N*, a nerve.

a diameter of about two mm. No apparent pigmentation or mole had been noticed previously to seven years ago. The mole was always firm and did not present any signs of irritation or inflammation.

Six months previous to the removal of the mole by operation (*i.e.*, eighteen months ago) it was accidentally scratched, after which time it began to increase in size. A small scab formed over it. The writer then saw it and was asked his opinion concerning the lesion. A diagnosis of epithelioma was made. Thorough excision was done by Dr. Halsted twelve months ago. The patient is twenty-seven years old, about 5 feet 9 inches in height, and of a healthy, wiry build.

The histological features are of great interest since the sections prepared by Dr. Young showed very beautifully all stages of commencing malignant downgrowth of the epithelium of the epidermis (Fig. 4, C). The excessive increase in pigment granules and pigment masses (P., Fig. 4) apparently keep pace with the increase in volume of the epi-

FIG. 4.



Section of a melanocarcinoma beginning in a mole (Case II.). C, the malignant downgrowth of epithelium from the epidermis; P, the pigment granules and masses; S, sebaceous gland; D, sweat-duct; G, sweat-glands; H, oblique section of a hair.

thelium. The increase in pigment of the carcinoma has probably been due to a malignant progress of the same process which has produced the increased pigment present in the epidermis of the mole itself; in other words, the greater portion of the pigment of the carcinoma has not been derived from the pigment in the corium of the mole. Some slight remains of the unaffected structure of the mole can be seen between the epidermal downgrowths; clumps of pigment belonging to the mole structure are also found in the corium. In this case there is not the slightest doubt that the malignant growth commencing in a mole is of epidermal origin and is, therefore, a melanotic carcinoma.

In view of the fact that the primary lesion in the first case (in the negro) may have originated in a mole and that in the second (Dr. Young's case) we had an undoubted carcinoma commencing in a pigmented mole, it was deemed of interest to undertake the study of the histology of pigmented moles with especial regard to their origin.

Four pigmented moles from adults and one from a child twenty-one months old were excised from living persons and examined.

Virchow, v. Recklinhausen, Demiéville, Post, Green, Bauer, Ribbert, and others have expressed the opinion that moles are of connective-tissue or endothelial origin, whereas, as has been said before, Unna advanced the view that they are derived from the epidermis. Unna came to his conclusions as the result of examining moles from infants and children, and was able to demonstrate the connection between the cells which make up the mole and the epidermis covering it. He holds that the epidermal downgrowths become gradually "snared off" so that in the adult no connection is seen between the structure of the mole and the epithelium. Scheuber has just lately confirmed Unna's observations. These two authors are, therefore, of the opinion that malignant pigmented growths arising from moles are not melanosacromata but melanocarcinomata.

Fordyce<sup>1</sup> says that many tumors which were formerly considered to be sarcomata were undoubtedly examples of pigmented carcinoma, but agrees that it is impossible to say clinically whether a given pigmented growth is a cancer or a sarcoma.

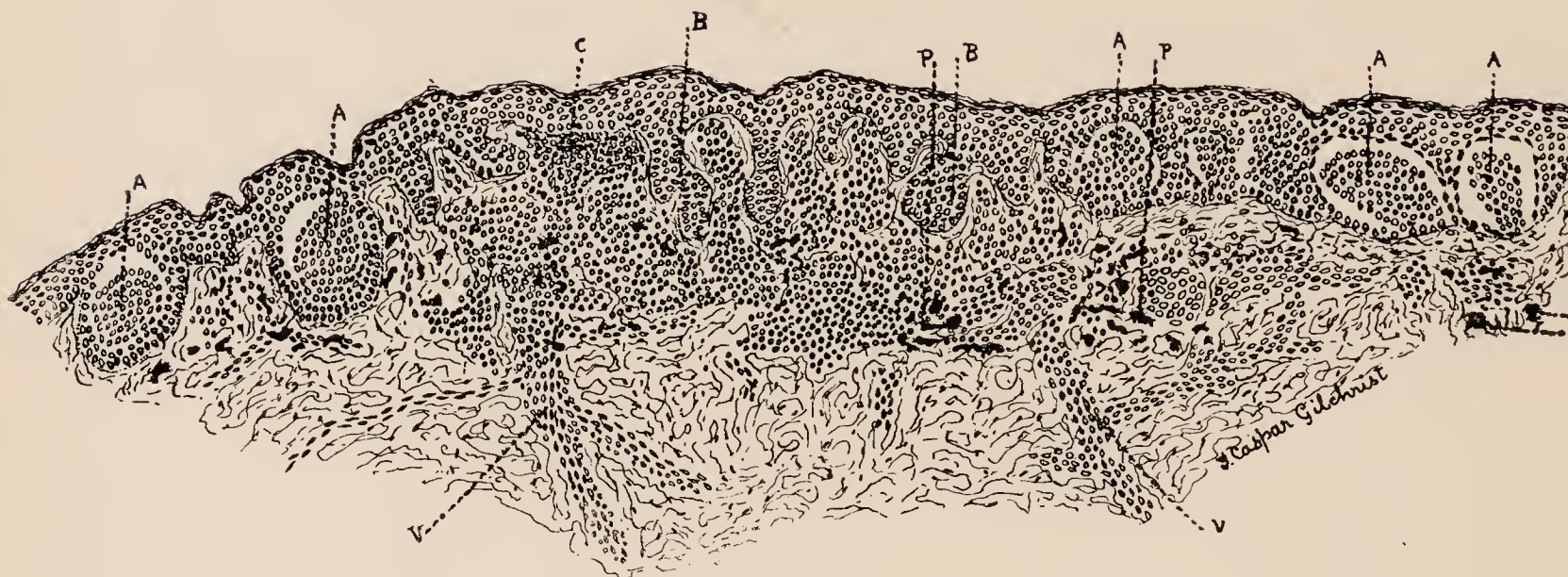
#### HISTOLOGY OF MOLES.

A small, deeply pigmented mole was removed from the abdomen of a child twenty-one months old. The section presented the following features (Fig. 5 represents one of the sections): The horny layer consists of only two or three flattened strands; the stratum granulosum is represented by one layer of cells and the rete by three or four layers of cells over the papillæ. Some very interesting features are seen in the epidermis. There are what appear at first sight to be a number of fairly large vesicular spaces (*A.A.* Fig. 5, *A.C.* Fig. 7), situated in the epidermis and containing collections of epithelial cells, with numerous pigment granules between and within the cells. As many as seven collections were seen in one section. In many sections these collections of cells are connected below with a continuation

<sup>1</sup> "American Textbook of Genito-Urinary Diseases, Syphilis, and Diseases of the Skin," p. 1044.

of the rete layer of the epidermis as a single layer of cells (*B. Fig. 7*); in other places these masses have become detached from the epidermis at the lower portion of the lateral aspects (*C. D. Fig. 7*, and *A. Fig. 6*) and retain their situation in the upper portion of the corium with a slight space between them and the epidermis above and laterally. In other places there can be noticed deeper prolongations of the interpapillary portion of the epidermis (*B.B. Fig. 5*, *B. Fig. 6*, and *D. Fig. 7*); the lower half is being "snared" off (as Unna expresses it) or constricted off. In other sections one can see this constriction still more marked (*Fig. 6 B*). The lower portions, which are constricted off, are also deeply pigmented (*C.D. Fig. 6*). When adjoining collections of cells, as represented in *Fig. 7* become detached,

*Fig. 5.*



Section of a pigmented mole excised from a child 21 months old. *A*, shows the collection of epithelial cells being detached from the epidermis; *B*, the constricting off of portions of epidermis; *C*, confluent masses of epithelial cells; *P*, pigment; *V*, blood-vessels.

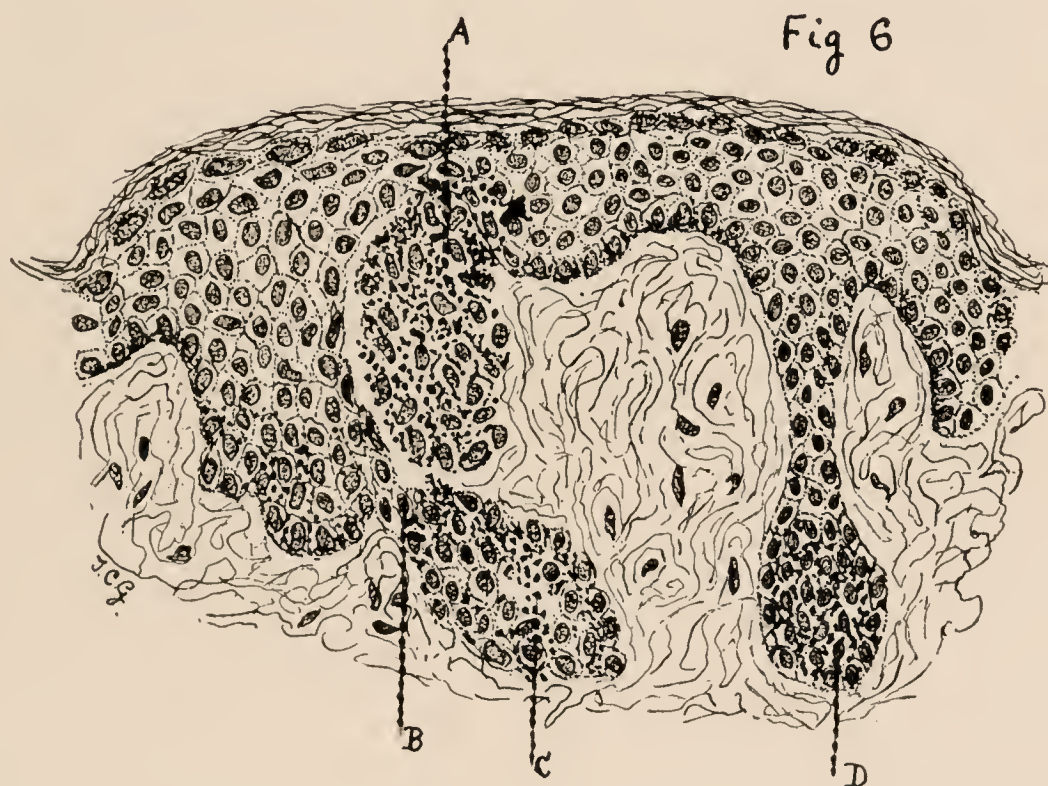
and the interpapillary portion becomes constricted off (*D. Fig. 7*), the two collections of cells in the further process become joined together so that large confluent masses of epithelium occupy the upper portion of the corium (*C. Fig. 5*).

Since the collection of cells just referred to become detached from the epidermis and the snaring-off process is carried on as well, it is thus seen that *in this mole* by far the largest portion of the structure of the mole is derived from the epidermis. The deeper portions of the mole structure consist simply of the lower portion of the same masses of epithelial cells.

In one section a collection of cells was seen enclosed in the wall of a hair-follicle and one in the lower half of the epidermal portion of a sweat-duct. Normal skin was included in the section so that a comparison could be made. The epidermis over the mole was not so deeply pigmented as the corium except in the places where collections of epidermal cells were being detached.

Comparatively large masses of pigment were distributed throughout the structure of the mole and the epidermis covering it. Some of the pigment masses in the corium are equal to ten times the size of the adjoining epithelial cells (Fig. 5, *P*). In the deepest portion of the corium there are collections of cells round the vessels which are of a different nature to those which make up the structure of the mole (*V.V.* Fig. 5).

It is thus seen in the section from this mole that one can follow the



From the same mole, showing the constricting off of portions of epidermis, *B*, *D*, and detachment of masses of cells, *A*, *C*.

stages of the detachment and constricting off of masses or collections of epithelial cells from the epidermis and that these masses are deeply pigmented and go to form the structure of the mole itself. The mole is, therefore, of epidermal and not of dermal origin.

Sections were made from numerous other pigmented moles taken from adults and one could occasionally still see traces of the snaring-off process.

#### SUMMARY.

The two cases described were instances of malignant melanotic growth commencing in the skin. The first case was followed by

numerous metastases, especially in the skin, but the superficial lymphatic glands were unaffected even up to the time of death. The cutaneous metastases were first deposited in the subcutaneous fat (Fig. 3, *M*).

The second case began in a pigmented mole on the face of a young physician and was excised in an early stage of its growth. The microscopical appearance left no doubt as to the origin of the malignant overgrowth in the epidermis—it was unquestionably a melano-carcinoma (Fig 4).

A small pigmented mole was excised from the skin of the abdomen of a child twenty-one months old and the sections demonstrated the

Fig. 7.



From the same mole, showing collections of epidermal cells separating from the epidermis. Collection *A* is still attached below *B* by one layer of cells. Collection *C* is almost detached below and the portion *D* is quite detached from the epidermis.

manner in which the collections of epithelioid cells which go to make up the structure of the mole were originally derived from the epidermis, namely, by detachment of collections of epithelial cells and by the constricting off of the lower portions of the interpapillary processes (Figs. 5, 6, 7).

Pathologists had, one might say, universally accepted Virchow's views that the cells of which the mole chiefly consisted were of connective tissue or endothelial origin until Unna, after following out the histogenesis of moles, concluded that these epithelioid cells were of epidermal origin. The present investigations confirm Unna's views.

Since the epithelioid cells which make up the stricture of the mole are of epidermal origin any malignant growth springing from these cells should be regarded as of a carcinomatous and not sarcomatous nature. Our second case supports this view.

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